

in Fig. 5A as issued as well as in the original Fig. 5A as filed.

## '554 Patent - Fig. 5A As Issued

- Three main errors that need correction:
  - LE is incorrect (should be VQ)
  - F in box is incorrect (should be outside)
  - codon for I (ATT) should be ATC

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FIG. 5A

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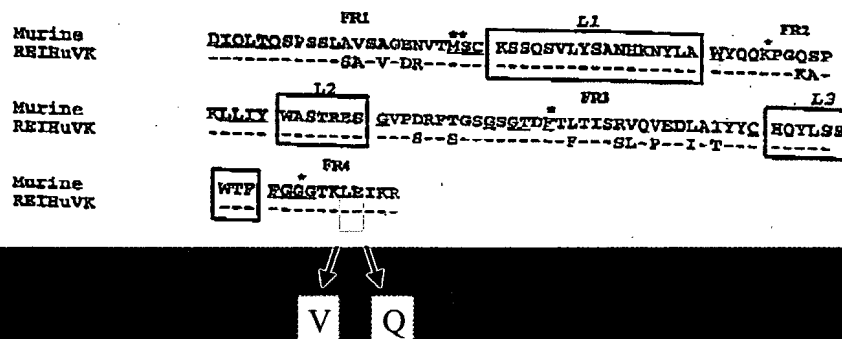
GACATTGAGCTGACCCAGTCTCCATCATCTCTGAGCGCATCTGTTGGAGATAGGGTCACT
1 CTGTAGTCGACTGGGTCAGAGGTAGTAGAGACTCGCGTAGACAACCTCTATCCAGTGA
D I O L T Q S P S S L S A S V G D R V T -
61 ATG ATC GTCCAGTCAAAGTGTTTATACAGTGCAAATCACAAGAACTACTTGGCC
TACTCGACATTGAGGTCAGTTTCACAAAATATGTCAGGTTAGTGTCTTGATGAACCGG
CDR1
M S C K S S Q S V L Y S A N H K N Y L A -
121 TGGTACCAGCAGAAACCAGGGAAGCACCTAAACTGCTGATCTACTGGGCATCCACTAGG
ACCATGGTCGTCTTTGGTCCCTTCGTGGATTGACGACTAGATGACCCGTAGGTGATCC
CDR2
W Y Q Q K P G K A P K L L I Y W A S T R -
181 GAATCTGGTGTCCCTTCGCGATTCTCTGGCAGCGGATCTGGGACAGATTTACTTTCAAC
CTTAGACCACAGGGAAGCGCTAAGAGACCGTCGCCTAGACCTGTCTAAAATGAAAGTGS
E S G V P S R F S G S G S G T D F T F T -
241 ATCAGCTCTCTTCAACCAGAAGACATTGCAACATATTATTGTCACCAATACCTCTCTCTCG
TGGTCTTCTTACCTTATAATAACAGTGGTTATGGAGAGGAGC
CDR3
W T F P E V A Q Y Y C H Q Y L S S -
301 TGGAGTTTCGGTGGAGGGACCAACTGGGATCAACGT
ACCTGCAAGCCACCTCCCTGGTTCGACCTCTAGTTTGCA
W T F G G G T K L E I K R
339

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## '554 Patent - Fig. 1A

Fig. 1A.



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## '554 Patent - Fig. 5A As Filed

- No IKR (instead ICRSP), but changed to IKR during prosecution - argued that Fig. 1 as filed showed IKR
- did have VQ, but changed to LE during prosecution - argued that Fig. 1 as filed showed LE
- did have erroneous I codon (ATT)

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As summarized in the slide immediately above, arguments were made for certain sequence changes based on Fig. 1 during prosecution of the parent patent. The change to IKR was correct, but the change of VQ to LE was incorrect (at the time these arguments were made in the parent patent, LE was thought to be correct). As shown below, however, there are several reasons why one of ordinary skill in the art would have realized that VQ should not have been changed and that IKR was a correct change. In addition, as discussed



“F.” Additionally as noted above, original Fig. 5A contained the “VQ” in FR4 “FGGGTKVQICRSP.” These two amino acid sequences were incorrectly changed to the corresponding murine sequences during prosecution of the ‘554 patent. As noted above, SEQ ID NO:21 (SEQ ID NO:18 as originally filed) supports this sequence.

## ‘554 Patent - Support for Changes

- Oligo SEQ ID NO: 18 (issued SEQ ID NO: 21):

~~CAC~~CGGCAGATCTGCACCTTGGTCCCTCCACCG

G CCA CCT CCC TGG TTC CAC GTC TAG ACG GC~~CA~~

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## ‘554 Patent - Support for Changes

- Oligo SEQ ID NO: 18 (issued SEQ ID NO: 21):

- ~~CAC~~CGGCAGATCTGCACCTTGGTCCCTCCACCG

- this oligo lines up with the bottom strand in reverse direction of Fig. 5A:

- G G G T K V Q I C R

- C GGT GGA GGG ACC AAG GTG CAG ATC TGC CGG TC

- G CCA CCT CCC TGG TTC CAC GTC TAG ACG GC~~CA~~

- underlined sequence shows the BglIII site
- Fig. 5A as filed contains the intermediate PCR product sequence (ICR)

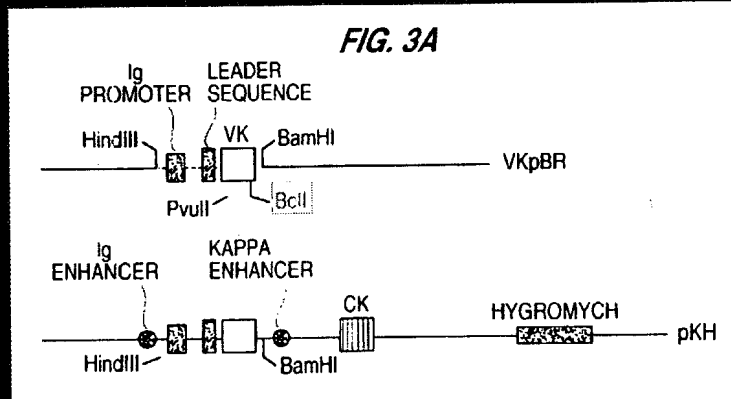
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## '554 Patent - Support for Changes

- Support for IKR & further support for VQ
- BclI site used in staging vector (col. 15, lines 21-26; p. 28, lines 1-6) introduces the first A of K codon & BglIII requires A of Q codon:
  - the previous BglIII cut is depicted as follows:
    - Q I C R S P
    - CA GATC TCC CGG TCT CCC
  - the product to the left of the red line above is then ligated into the BclI site of the staging vector:
    - Q I K R
    - CA GATC AAA CGT

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## '554 Patent - Support for Changes



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- a C (as shown in original Fig. 5A) would be incompatible with use of BclI (codon must start with a T), but a K (as shown in original Fig. 1A) is compatible (codon starts with A)
- one of ordinary skill in the art would resolve the conflict between IKR (original Fig. 1A) and ICRSP (original Fig. 5A) based on the restriction sites & oligo SEQ ID 18 in favor of IKR
- this is not inconsistent with choosing VQ from Fig. 5A because that choice is also dictated by the restriction sites which require Q and oligo SEQ ID 18
- BglII/BclI sites are consistent with the sequence of oligo SEQ ID 18 (issued SEQ ID 21) - anchor for all changes

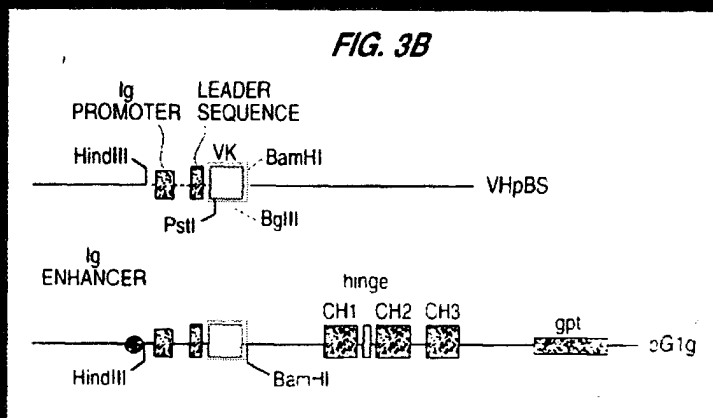
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## '554 Patent - Support for Changes

- Further support comes from Orlandi
- intron removal in expression vector creates final IKR subsequence
  - "The VK and VH sequences for cLL2 or hLL2 can [be] amplified by PCR as described in Orlandi et al. (*Proc. Natl. Acad. Sci., USA*, 86:3833 (1989)) which is incorporated by reference" (col. 8, lines 1-4; p. 15, lines 3-6)
  - Orlandi at p. 3834, right column, lines 6-9, and in Fig. 2 legend cites to Riechmann (*Nature*, 332(1988): 323-327), for explanation of non-coding regions
  - Riechmann (p. 324, legend of Fig. 1), in turn, cites to Hieter (*Cell*, 22(1980): 197-201) for an explanation of "the 3' non-coding sequence taken from a human J<sub>H</sub>-region sequence"

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## '554 Patent - Fig. 3B



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## '554 Patent - Support for Changes

- HindIII/BamHI fragment was subcloned into the expression vector, pKh, where it was linked to the genomic DNA for Ck, including introns and exon:
- ... AAACgt ... ggaacc ... **agCAACTGTC** ...
- ... K ... T V ...
- UPPERCASE, exon; lowercase, intron; Underlined, BamHI site; **bold**, splicing donor and acceptor
- Blue shows the sequence from VKpBR and red shows that from pKh. Note that the coding sequences for Vk and Ck are discontinued. The stop codon is at the end of Ck sequence.

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... .. AAACgt... ..ggttsc... ..aaatgtt... ..

... .. AAACGAACCTT... ..

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## '554 Patent - Support for Changes

- After the precursor RNA has been transcribed according to the genome sequence, a splicing event removes the intron sequence and ligates the Vk segment to Ck, resulting in mRNA, which will look like this:

- ... .. AAA CGA ACU CUC... ..

- ... .. K R T V ... ..

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## '554 Patent - Support for Changes

GenBank ACCESSION J00241

AUTHORS Hieter, P.A., Max, E.E., Seidman, J.C., Maizel, J.V. Jr. and Leder, P.  
JOURNAL Cell 22 (1 Pt 1), 197-207 (1980)

Insertion: 1-333

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1  ttctaaactc tgagggggc ggatgaagtg gccattttt gctaaagca ttgagttac
61  tgcagggtca gaaagcctg caagccctc agaatgggtg caagagctc caacaaaca
121  atttagaact ttattaaaga atagggggaa gctaggaaga aactcaaac atcaagattt
181  taaataagct tcttggtctc ctgtgtatca ttatctggga taagcatgct gttttctgtc
241  tgtccctaac atgcccgtgtg attatccga acaaacacac caaggggag aattttgtta
301  cttaaaacac atctgtgttg ctcttttctt cag gctgcaaca tctgtcttca
361  tcttcccgcc atctggtgag cagtggaaat ctggaaactg ctctgttgtg tgcctgctga
421  ataaacttca tccagagag gccaaagtac agtgggaagt ggataacgac ctccatctgg
481  gtaactccca ggagagtgct acagagcagg acagcaagga cagcaactac agcctcagca
541  gaacctgac gctgagcaaa gcaagactag agaaacacaa agtctacgac tgggaagtca
601  cccatcaggg cctgagctgg ccgctcaca agagcttcaa aaggggagag tgttagaggg
661  agaagtggcc ccaactgctc ctcaagtcca gctgacccc ctccatctct ttggctcttg
721  aaccttttct caaggggac ctacccctat tggggctcct cagctcatct ttaactcac
781  cccctctctc ctcttgggt ttatttatgc taatgttggg ggagatgca taaataaagt
841  gaattcttgc aactgtggtt tctctcttct ctcaatttaa taattattat ctgttgttta
901  ccaactacac aattctctct ataggggact aatatgttag taactcttag gggcataacc
961  atttataaaa atcaactctc attctatttt acctatctat ctctggaag acagctctcc
1021 ctcaaacaca caagccttct gtcctcacc tcccctgggc cgtggtagga gagacttgc
1081 tcttgttttt cccctctcga gcaagccctc atagtccttt ttaagggtag caggtcttac
1141 ggtctatat ctcttgatc aattccctg gaataacaa aggaatttt tcaaaagaa
1201 gaaactgc

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As noted by the explanation above, the sequence in FR4, "ICRSP" of the light chain variable region in Fig. 5A represents an intermediate product of the staging vector before insertion into the expression vector, pKH, as shown in Fig. 3A.

## '554 Patent - Support for Fig. 5A

- Support for correction of 1 codon
  - "ATT" should be "ATC" as shown in Riechmann (*Nature*, 332(1988): 323-327, at Fig.1b)
  - Orlandi, however, shows ATT

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The scientific publications that are referred to above will be provided to the Examiner under separate cover.